REMARKS

In the Office Action, the Examiner (1) maintained the indefiniteness rejection under 35 U.S.C. §112, second paragraph against claim 47, (2) maintained the written description rejection under 35 U.S.C. §112, first paragraph against claims 10-14 and 41-50, and (3) maintained the anticipation rejection under 35 U.S.C. §102(b) against claims 10-14, 41-43 and 45-50 over Kozaki et al. (Microbial Pathogenesis, 1998, 25:91-99). The Examiner withdrew the anticipation rejection against claim 44. Each maintained rejection is addressed separately below. In view of the amendments noted above and the remarks below, applicants respectfully request reconsideration of the merits of this patent application.

The claim amendments provided here introduce no new issue and the Office Action cited no new art. The subject matter of the amended claims has already been considered by the Examiner in the context of 35 U.S.C. §112, first and second paragraphs and *vis a vis* the same reference in the anticipation context. Therefore, the amendments and remarks presented here are believed to be appropriate for entry and consideration in after final practice.

No extension of time is believed to be necessary and no fee is believed to be due in connection with this response. However, if any extension of time is required in this or any subsequent response, please consider this to be a petition for the appropriate extension and a request to charge the petition fee to Deposit Account No. 17-0055. No other fee is believed to be due in connection with this response. However, if any fee is due in this or any subsequent response, please charge the fee to the same Deposit Account No. 17-0055.

Indefiniteness rejection under 35 U.S.C. §112, second paragraph

The Examiner maintained the indefiniteness rejection against claim 47. In response to the amendment (to claim 47) and arguments provided in the previous response, the Examiner asserts that a claim should be able to stand alone and applicant should not have to provide an explanation to one skilled in the art for them to understand the limitations in the claims.

Applicants respectfully note that it is settled law that a dependent claim incorporates all limitations of the claim(s) on which the dependent claim depends. In this regard, claim 47 depends on claim 45 which in turn depends on claim 10. Therefore, claim 47 incorporates all of the limitations in claims 10 and 45. As it is clear from claim 10, what is being claimed is a

complex of a ligand and a polypeptide (the polypeptide is defined in detail in claim 10), not an organism such as a rat, mouse or human. Claim 45 as amended further limits the ligand to an antibody that binds to the BoNT/B-binding domain. Accordingly, it is clear that claim 47 is directed at a complex of the polypeptide and its antibody rather than an organism such as a rat, mouse or human. It is well understood that a dependent claim incorporates all limitations of the claim(s) on which the dependent claim depends and therefore a skilled artisan will certainly understand the scope of claim 47 as provided above. No explanation is required.

In addition, it is clear that claim 47 does not cover an organism such as a rat, mouse or human also because claim 47 specifies that the complex is located in a mammal. If claim 47 covers a rat, how can a rat be located in a rat?

To facilitate prosecution, claim 47 has been rewritten in independent form and it is clear that claim 47 is directed at a complex of a ligand and a polypeptide located in a mammal.

Withdrawal of the indefiniteness rejection is respectfully requested.

Written description rejection under 35 U.S.C. §112, first paragraph

The Examiner maintained the rejection against claims 10-14 and 41-50 as failing to comply with the written description requirement. Without agreeing with the rejection, applicants have amended claim 10 to the scope of dependent claim 41. As a result, claims 11-13, 41, 50, 52-54, 56, and 66 are canceled. Applicants reserve the right to pursue the canceled subject matter in a continuation application.

As amended, the polypeptide in the claimed complex has been limited to one that comprises a murine synaptotagmin II BoNT/B-binding domain (for mouse: amino acids 40-60 of SEQ ID NO:7; for rat: amino acids 40-60 of SEQ ID NO:9) or a fragment of a mouse or rat synaptotagmin II homolog that corresponds to amino acids 40-60 of SEQ ID NO:7 or 9. Applicants respectfully submit that the written description requirement for the claims as amended is met.

As the present application provided the amino acid sequences of SEQ ID NO:7 and 9, the written description requirement for claim 14 is clearly met.

With respect to "a fragment of a mouse or rat synaptotagmin II homolog that corresponds to amino acids 40-60 of SEQ ID NO:7 or 9" recited in the other claims at issue (e.g., claim 10),

applicants respectfully note that to comply with the written description requirement, the specification only needs to describe in detail that which is new (*see Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367 (Fed. Cir. 1986)). Regarding gene sequences in particular, the Federal Circuit has held that recitation of known gene sequences and essential regions or structures thereof is not required to satisfy the written description requirement.

In *Capon v. Eshhar*, 418 F.3d 1349 (Fed. Cir. 2005), the court stated that "[t]he chimeric genes here at issue are prepared from known DNA sequences of known function. ... The Board erred in holding that the specifications do not meet the written description requirement because they do not reiterate the structure or formula or chemical name for the nucleotide sequences of the claimed chimeric genes."

In *Falko-Gunter Falkner v. Inglis,* 448 F.3d 1357 (Fed. Cir. 2006), the court rejected the petitioner's reliance on *Regents of the University of California v. Eli Lilly & Co.*, 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997), for the proposition that the written description requirement was not met because Inglis did not describe "essential regions" of any poxvirus. "However, it is the binding precedent of this court that *Eli Lilly* does not set forth a *per se* rule that whenever a claim limitation is directed to a macromolecular sequence, the specification must always recite the gene or sequence, regardless of whether it is known in the prior art," the court noted.

The court further held that "a requirement that patentees recite known DNA structures, if one existed, would serve no goal of the written description requirement. ... Indeed, the forced recitation of known sequences in patent disclosures would only add unnecessary bulk to the specification. Accordingly, we hold that where, as in this case, accessible literature sources clearly provided, as of the relevant date, genes and their nucleotide sequences (here "essential genes"), satisfaction of the written description requirement does not require either the recitation or incorporation by reference (where permitted) of such genes and sequences."

In the case of the present application, synaptotagmin II is a well known protein and the amino acid sequences of synaptotagmin II from a number of species are known and well conserved. The structure of synaptotagmin II is also conserved and well known in the art. For example, synaptotagmin II proteins from rat, mouse, and human are highly conserved (e.g., over 90% identical at the BoNT/B binding domain) and they all contain a luminal domain, a

transmembrane domain, and a cytoplamic domain, which contains two C2 domains: C2A and C2B linked by a linker region (*see* paragraph [0007]).

What is new for the present invention is that the inventors pinpointed the BoNT/B binding domain of synaptotagmin II proteins through a series of structural and functional experiments (*see e.g.*, paragraphs [00067], [00068], [00071]-[00073], [00077], and [00078]). With the above new feature of the invention fully described in the specification and the synaptotagmin II proteins from a number of species well known in terms of their conserved amino acid sequences and structure, the written description requirement for "a fragment of a mouse or rat synaptotagmin II homolog that corresponds to amino acids 40-60 of SEQ ID NO:7 or 9" is met. In this regard, the BoNT/B binding domain on a rat or mouse synaptotagmin II homolog can be readily recognized by a skilled artisan, for example by using an amino acid sequence alignment program (e.g., the widely used ClustalW web software at "http://www.ch.embnet.org/software/ClustalW.html" with the default settings) to identify the region that corresponds to amino acids 40-60 of SEQ ID NO:7 or 9, especially given that the amino acid sequences and structures of synaptotagmin II proteins are highly conserved.

Lastly, with respect to comment C) on page 8 of the present office action, applicants note that applicants did not say in the previous response that the subject matter of "synaptotagmin II fragments" has been deleted. Rather, applicants said that the subject matter of "BoNT/B fragments" has been deleted. This was in response to the Examiner's written description rejection over "botulinum toxin fragments" raised in the previous office action (see page 6, lines 1-3 of the last paragraph in the previous office action).

For all of the above reasons, it is respectfully submitted that the written description requirement for the claims as amended is met.

Anticipation rejections under 35 U.S.C. §102 (b)

The Examiner maintained the rejection against claims 10-14, 41-43 and 45-50 under 35 U.S.C. §102(b) as being anticipated by Kozaki et al. (Microbial Pathogenesis, 1998, 25:91-99). Applicants had argued in the previous response that Kozaki et al. do not specifically teach that BoNT/B or an antibody disclosed therein binds to amino acids 40-60 of synaptotagmin II as

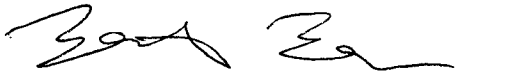
required by the claims at issue. However, the Examiner asserts that Kozaki et al. teach that BoNT/B and antibody 3A2 bind to amino acids 40-60 of synaptotagmin II.

Applicants strongly disagree. Applicants could not find and the Examiner failed to point to anywhere in Kozaki et al. where "amino acids 40-60 of synaptotagmin II" is specifically mentioned. The Examiner asserts that MBP-Stg2N of Kozaki et al. (containing amino acids 1-87 of the rat synaptotagmin II) includes the N-terminal domain (amino acids 1-60) as well as the transmembrane region (amino acids 61-87). This is acknowledged. The Examiner further asserts that Kozaki et al. teach that BoNT/B and a ganglioside binding domain antibody 3A2 bind to the ganglioside binding domain of rat synaptotagmin II, which includes amino acids 53-79. This is not accurate. As provided in the present application in paragraph [0024] (page 8) at lines 7-10, the ganglioside binding domain of rat synaptotagmin II is amino acids 61-87, not 53-79. The ganglioside binding domain of rat synaptotagmin I (not II) is amino acids 53-79. Therefore, based on the logic of the Examiner, it follows that Kozaki et al. disclosed that BoNT/B and the ganglioside binding domain antibody 3A2 bind to amino acids 61-87, not 40-60, of rat synaptotagmin II. Withdrawal of the rejection is respectfully requested.

Summary

Having addressed each rejection maintained by the Examiner by claim amendments and arguments, the claims as amended are believed to be in condition for allowance and a Notice of Allowance is respectfully requested. Should any issues remain outstanding, the Examiner is invited to contact the undersigned at the telephone number appearing below if such would advance the prosecution of this application.

Respectfully submitted,



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